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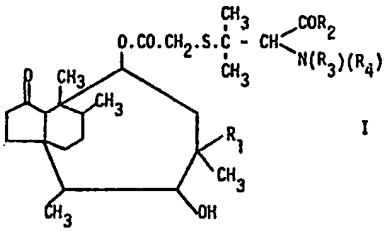
C2C
(71) Applicant
Sandoz Limited
(Switzerland)
35 Lichtstrasse
CH-4002 Basle
Switzerland
(72) Inventor
Heinz Berner
(74) Agent and/or Address for Service
B A Yorke and Co
98 The Centre
Feltham
Middlesex TW13 4EP

(54) Pleuromutilin derivatives

(57) Compounds of formula I



I

wherein

R_1 represents ethyl or vinyl,

R_2 represents lower alkoxy, amino, lower alkylamino which may be unsubstituted or substituted by amino, lower alkylamino, di-(lower)-alkylamino or hydroxy, di-(lower)-alkylamino or a five or six membered, saturated heterocycle which contains one or two nitrogens as heteroatoms and which may be unsubstituted or substituted by lower alkyl and

R_3 and R_4 represent, independently, hydrogen or lower alkyl, in free base or acid addition or quaternary salt form,

exhibit pharmacological activity, particularly against bacteria and obligatory anaerobes, and can be incorporated into chemotherapeutic compositions.

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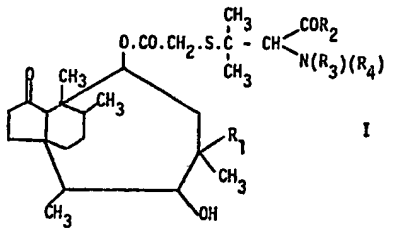
SPECIFICATION

Pleuromutilin derivatives, processes for their production and their use as pharmaceuticals

The present invention concerns pleuromutilin derivatives, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as antibacterially active antibiotics and against obligatory anaerobes.

More particularly the invention concerns compounds of formula I



I

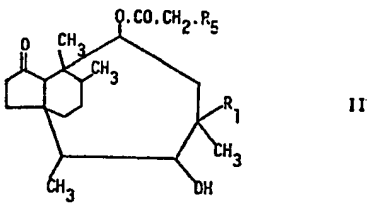
wherein

R_1 represents ethyl or vinyl

R_2 represents lower alkoxy, amino, lower alkylamino which may be unsubstituted or substituted by amino, lower alkylamino, di-(lower)-alkylamino or hydroxy, di-(lower)-alkylamino or a five or six membered, saturated heterocycle which contains one or two nitrogens as heteroatoms and which may be unsubstituted or substituted by lower alkyl and

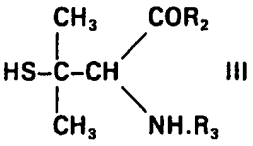
R_3 and R_4 represent, independently, hydrogen or lower alkyl, in free base or acid addition or quaternary salt form.

The compounds of formula I can be obtained by reacting a compound of formula II



II

with a compound of formula III



III

whereby R_1, R_2 and R_3 are as defined for formula I and R_5 represents chlorine, bromine or OSO_2R_6 wherein R_6 is alkyl or aryl and if desired further mono- or di-alkylating a compound thus obtained wherein R_3 represents hydrogen or further mono-alkylating a compound thus obtained wherein R_3 represents lower alkyl.

Reaction of II with III is carried out in conventional manner. for example by dissolving the compound of formula III in a solution of sodium in an anhydrous lower alkanol such as ethanol or methanol and then adding the compound of formula II in an inert solvent such as aliphatic ketone e.g. methylethylketone or acetone. Reaction temperatures lie e.g. between room temperature and boiling point of the the reaction mixture in particular 25° to 55°C.

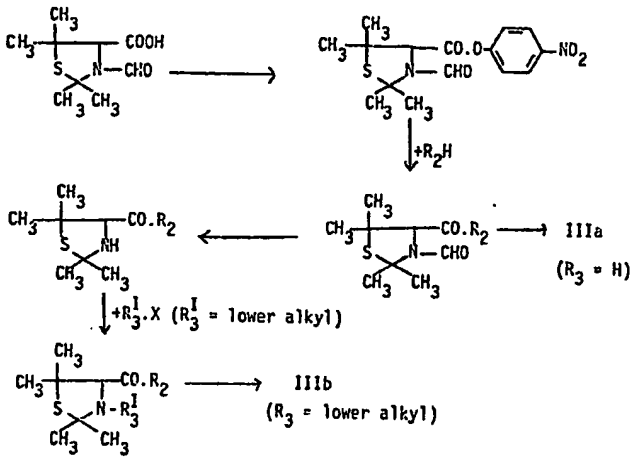
Alkylation of the reaction product is carried out in conventional manner for example as described in C.A. Bühler and D.E. Pearson, Survey of Organic Chemistry, Wiley Interscience. The degree of alkylation depends i.a. on the quantity of alkylating agent employed. Monoalkylated products are preferably obtained by employing an equivalent quantity of alkylating agent, dialkylated products by reaction with an excess of alkylating agent.

The end products can be isolated and purified according to known methods.

The compounds of formula I may be recovered in free base or acid addition or quaternary salt form in conventional manner. Free base forms can be converted in conventional manner into salt forms and vice versa.

The intermediate compounds of formulae II and III are either known or are obtainable analogously to known methods. The compounds of formula III can be obtained for example

according to the following reaction scheme employing conditions appropriate for the reaction involved.



The compounds of formula I and the corresponding starting materials contain asymmetric carbon and may thus exist in the form of diastereomeric isomers and mixtures thereof which may be separated in conventional manner. Use of optically active starting materials will lead to the corresponding end products. The invention concerns both isomers and mixtures thereof and reference is made to the latter unless otherwise stated. Compounds in substantially "D" form are of particular interest.

The compounds of formula I exhibit chemotherapeutic activity. In particular they exhibit antimicrobial activity as indicated *in vitro* in series dilution tests using various bacterial strains such as e.g. Staph. aureus, -epidermidis; Strept. pyogenes, -aronson, -pneumoniae, -faecalis; Aerococcus viridans; Haemophilus spp. and Neisseria gonorrh. at concentrations between 0.06 and 50 μg/ml and *in vivo* in tests on mice. In particular a inhibitory activity is indicated in tests using Mycoplasmas e.g. Mycoplasma hominis, Mycoplasma pneumoniae and Ureaplasma urealyticum as well as Chlamydien e.g. Chlamydia trachomatis at concentrations between 0.02 and 5 μg/ml The compounds of the invention are therefore indicated for use as antibacterially active antibiotics.

The compounds of formula I also exhibit activity against obligatory anaerobes as indicated *in vitro* in series dilution tests and *in vivo* in tests on mice. *In vitro* activity a concentration of 0.008 to 50 μg/ml was observed against various strains such as Bacteroides fragilis, Bacteroides thetaiotaomic, Bacteroides vulgatus, Sphaerophorus varius, Sphaerophorus freundii, Clostridium perfringens, Bacteroides melaninogenicus and Spaerophorus necrophorus.

In *in vivo* tests satisfactory results were obtained at dosages of from 10 to 300 mg/kg body weight p.o. or s.c.

The compounds are therefore indicated for use in combating infections caused by obligatory anaerobes.

An indicated daily dosage form is from about 0.1 to 3 g, especially 1 to 3 g and dosage forms suitable for internal administration comprise about 25 to 1500 mg of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition and quaternary salts. Such salt forms exhibit the same order of activity as the free base forms.

Examples of suitable acid addition salts are the hydrogen fumarate, fumarate, naphthalin-1,5-sulfonate and especially the hydrochloride.

The compounds may be administered orally or parentally and admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets, capsules or injectable preparations.

Such compositions also form part of the invention.

The invention therefore also concerns a method of combatting bacteria and obligatory anaerobes comprising administering to a subject in need of such treatment an effective amount of a compoumd of formula I or a chemotherapeutically acceptable acid addition or quaternary salt thereof and such compounds for use as chemotherapeutic agents, in particular anti-bacterially active antibiotics and agents against infections caused by obligatory anaerobes.

Lower alkyl (or alkoxy) is particularly C_{1-4} alkyl (or alkoxy) and in the case of R_3 and R_4 especially methyl (methoxy). Examples of heterocycles as R_2 are pyrrolidino, imidazolidino, pyrazolidino, piperidino and especially piperazino, these may be substituted by lower alkyl, particularly methyl.

A particular compound group is that wherein in formula I

R_2 represents lower alkoxy, amino, lower alkylamino unsubstituted or substituted by hydroxy, amino or di-(lower)-alkylamino, di-(lower)-alkylamino, piperazino, 4-(lower)-alkylpiperazino, and R_1, R_3 and R_4 are as defined in formula I, in free base or in acid addition or quaternary salt form.

A further group covers compounds of formula I wherein

R_2 represents lower alkoxy, amino, optionally amino or hydroxy substituted lower alkylamino or a di-(lower)-alkyl amino group and

R_1, R_3 and R_4 are as defined under formula I in free base or in acid addition or quaternary salt form.

A further group covers compounds of formula I wherein

R_2 represents lower alkoxy, amino, optionally amino or hydroxy substituted lower alkyl amino, a di-(lower)-alkyl amino group or a 5- or 6-membered saturated heterocycle which contains one or two nitrogens as heteroatoms and which may be unsubstituted or substituted by lower alkyl, in free base or in acid addition or quaternary salt form.

A further group covers compounds wherein

R_2 represents amino, lower alkylamino or alkoxy and

R_3 and R_4 represent independently hydrogen or lower alkyl especially methyl,

in free base or in acid addition or quaternary salt form.

Two particularly preferred individual compounds are 14–O-[(1-amino-1-methylaminocarbonyl-2-methylpropan-2-yl)-thioacetyl]dihydromutilin and its hydrochloride as well as particularly 14–O-[(1-amino-1-methylcarbonyl-2-methylpropan-2-yl)-thioacetyl]mutilin and its hydrochloride.

Example 1: 14–O-{[1-Amino-1-(2-hydroxyethan-1-ylaminocarbonyl)-2-methylpropan-2-yl]thioacetyl} mutilin-chloride

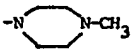
2 g of 3-Methyl-3-mercapto-2-aminobutyric acid-(2-hydroxyethyl)-amide, 4.63 g of pleuromutilin-22–O-tosylate and 3.73 g of tetrabutylammoniumhydrogensulfate are taken up in a heterogenous mixture of 45 ml 1N Na OH and 100 ml of dichloromethane. After 3 hours of reaction the dichloromethane phase is separated and worked-up. The crude product is further purified by chromatography over silica gel (eluant: CCl_3/CH_3OH 8/1) to obtain the amorphous title product.

Example 2: (D)-14–O-[(Amino-1-carbomethoxy-2-methylpropan-2-yl)-thioacetyl]mutilin-hydrochloride

4 g D-Penicillaminemethyl ester-hydrochloride are taken up in a solution of 0–92 g of sodium in 70 ml of methanol and allowed to stand for 1 hour at 25° to allow complete formation of the thiolate salt. To this solution is then added 10.6 g of pleuromutilin-22–O-tosylate dissolved in 100 ml of methylethylketone. After 24 hours of reaction at 25° the product is worked up conventionally and chromatographed over silica gel (eluant: toluene/ethylacetate: 1/1) to give the title product, m.p. 133°.

The following compounds may be obtained analogously or as otherwise hereinbefore described.

Ex.	R_1	R_2	R_3	R_4	Physical Data
3	C_2H_5	$-NH.CH_2CH_2OH$	H	H	amorphous
4	$-CH=CH_2$	$-NH_2$	H	H	-"-
5	-"-	$-NH.CH_3$	H	H	-"-
6	-"-	$-NH.CH_2CH_2.NH_2$	H	H	-"-
7	-"-	$-O.CH_3$	H	H	-"-(L)
8	-"-	$-O.CH_2CH_2CH_2CH_3$	H	H	-"-
9	C_2H_5	$-NH.C_2H_5$	CH_3	H	-"-

Ex.	R_1	R_2	R_3	R_4	Physical Data
10	C_2H_5	$-NH_2$	CH_3	H	amorphous
11	C_2H_5	$-NH.C_2H_5$	H	H	-"-
12	$CH=CH_2$	$-NH.CH_3$	CH_3	H	-"-
13	$CH=CH_2$	$-NH.CH_2CH_2.N(C_2H_5)_2$	H	H	-"-
14	C_2H_5	$-N(CH_3).CH_3$	H	H	-"-
15	C_2H_5	$-NH.CH_3$	H	H	-"-
16	$CH=CH_2$		H	H	-"-
17	C_2H_5	-"-	H	H	-"-
18	C_2H_5		H	H	-"-
19	$CH=CH_2$	$-OCH_3$	CH_3	H	-"-
20	C_2H_5	$-NH_2$	H	H	-"-

Example 21: 14–0-[(1-Dimethylamino-1-carbomethoxy-2-methylpropan-2-yl)thioacetyl]mutilin-hydrochloride

A solution of 1.04 g 14–0-[(1-amino-1-carbomethoxy-2-methylpropan-2-yl)thioacetyl]mutilin-hydrochloride, 0.29 g of potassium carbonate and 0.53 g of dimethylsulfate in 15 ml of dimethylformamide are warmed for 10 minutes at 100°. After conventional working up and chromatography on silicagel (eluant: hexane/ethylacetate: 3/2) the title compound is obtained.

The following compounds may be obtained analogously or as otherwise as hereinbefore described.

Ex.	R_1	R_2	R_3	R_4	Physical Data
22	$CH=CH_2$	$-OCH_3$	CH_3	H	amorphous
23	C_2H_5	$-NH.CH_3$	CH_3	H	-"-
24	C_2H_5	$-NH.C_2H_5$	CH_3	CH_3	-"-
25	C_2H_5	$-NH_2$	CH_3	CH_3	-"-
26	C_2H_5	$-NH_2$	CH_3	H	-"-
27	$CH=CH_2$	$-NH.CH_3$	CH_3	H	-"-

Example 28: (D)-14–0-(1-Amino-(1-methylaminocarbonyl)-2-methylpropan-2-yl)thioacetylmutilin hydrochloride

To a solution of 13.54 g D-penicillamine-acetone adduct (F. Asinger, K. Gluzek, Monatsh. f. Chemie *114*, 47–63 (1983)) in 300 ml of dioxane and 24 ml of pyridine are added under cooling 62.5 ml of phosgene in toluene. The reaction mixture is held for 1.5 hours at 25° and then reacted with 62.5 ml of a 8.03 molar solution of methylamine in ethanol. After 1 hr. the mixture is filtered and the filtrate washed with dichloromethane. Evaporation of the filtrate yields the protected methylamine which is recrystallised from di-isopropylether.

$\alpha_D^{20} = 136.8°$; $\alpha_{436}^{20} = 295.8°$ (both $CHCl_3$, C = 2g/100 ml)

Removal of the protecting group and reaction to the title compound using pleuromutilin tosylate take place analogously to examples 1 and 2.

$\alpha_D^{20} = 44°$; $\alpha_{436}^{20} = 114°$ (both $CHCl_3$, C = 11.4 mg/ml).

NMR-SPECTRA ($CDCl_3$)

Ex.	Spectrum
1	7.66 (m, 1H, NH-CO); 5.78 (d, 1H, H_{14}, $J_{H14,H13}$ = 9 Hz; 3.75 (m, 2H, CH_2-OH); 3.48 (m, 2H, -CH_2-NH-); 3.35 (s, 1H, -N-CH-CO); 2.31, 2.19 (s, s, 2 × CH_3, $(CH_3)_{18}$, $(CH_3)_{18}$); 0.9 (d, 3H, $(CH_3)_{17}$, J = 7.2 Hz); 0.72 (d, 3H, $(CH_3)_{15}$, J = 6.3 Hz).
2	5.78 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.72 (s, 3H, $COOCH_3$); 3.25 (s, 2H, S-CH_2-CO); 3.44 (s, 1H, N-CH-CO; 3.35 (m, 1H, H_{11}).
3	7.68 (m, 1H, NH); 5.62 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.74 (m, 2H, CH_2OH); 3.45 (m, 2H, -CH_2NH-); 3.38 (s, (1H, H_2N-CH-CO); 1.42, 1.45 (s, s, 2 × CH_3, -S-C$(CH_3)_2$-); 3.26 (s, 2H, S-CH_2-CO).
4	5.76 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 7.1 (b, 1H, NH); 3.35 (s, 1H, NH-CH-CO); 3.35 (m, 1H, H_{11}); 3.25 (s, 2H, S-CH_2-CO).
5	7.25 (m, 1H, NH); 5.78 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.35 (s, 1H, N-CH-CO); 2.85 (d, 3H, N-CH_3, J = 4.5 Hz); 1.5 (s, 6H, 2 × CH_3, -S-C$(CH_3)_2$-).
6	5.76 (d, 1H, H_{14}, $J_{H13,H14}$ = 8.1 Hz); 3.3 (s, 1H, N-CH-CO); 3.4-3.5 (m, 5H, -N-CH_2, H_{11}, S-CH_2-CO); 2.84 (t, 2H, -N-CH_2-, J = 6.3 Hz); 7.52 (m, 1H, NH).
7	5.78 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.72 (s, 3H, $COOCH_3$); 3.46 (s, 1H, N-CH-CO); 3.25 (s, 2H, S-CH_2-CO); 3.36 (d, 1H, H_{11}, $J_{H11,H10}$ = 6.3 Hz).
8	5.8 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 4.15 (t, 2H, O-CH_2, J = 6.3 Hz); 3.35 (m, 1H, H_{11}); 3.28 (s, 2H, S-CH_2-CO); 3.45 (s, 1H, N-CH-CO).
9	5.52 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); AB-System: ν_A = 3.29, ν_B = 3.42, S-CH_2-CO, J_{AB} = 15 Hz); 3.45 (m, 1H, H_{11}); 3.14 (m, 2H, N-*CH_2*CH_3); 2.82 (s, 1H, CO-*CH*-$NHCH_3$); 2.2 (s, 3H, N-*CH_3*).
10,26	7.15 (m, 1H, NH); 5.62 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.42 (m, 1H, H_{11}); 2.85 (s, 1H, CO-*CH*-$NHCH_3$); 2.40, 2.42 (s, s, 3H, $NHCH_3$); 1.43, 1.48, (s, s, 6H, S-C$(CH_3)_2$).
11	7.25 (b, 1H, NH); 5.63 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.32 (s, 1H, CO-CH-NH_2); 3.24 (AB-System, 2H, S-CH_2-CO, J_{AB} = 16 Hz).
12,27	7.0 (m, 1H, NH); 5.74 (d, 1H, H_{14}, J_{H14H13} = 9 Hz; 3.38, 3.40 (s, s, 1H, CO-CH-$NHCH_3$); 2.83 2.86 (s, s, 3H, CO-$NHCH_3$); 2.32, 2.44 (s, s, 3H, -$NHCH_3$).
13	7.45 (b, 1H, NH); 5.77 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.31 (s, 1H, CO-CH-NH_2); 3.3 (m, 2H, CO-NH-CH_2); 2.55 (q, 4H, N-(*CH_2*-CH_3), J = 8 Hz); 1.44 (s, 6H, S-C$(CH_3)_2$-); 1.02 (t, 6H, N-(CH_2-*CH_3*)$_2$).
14	5.61 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.86, 3.88 (s, s, 1H, CO-CH-NH_2); 3.43 (d, 1H, H_{11}, J_{H11H10} = 7 Hz); 3.24, 3.26 (s, s, S-CH_2-CO); 2.98, 3.15 (s, s, 2 × 3H, N-$(CH_3)_2$); 1.38 (s, 6H, S-C$(CH_3)_2$-).
15	7.3 (b, 1H, NH); 5.64 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.38 (s, 1H, CO-CH-NH_2); 3.45 (d, 1H, H_{11}, J_{H11H10} = 7 Hz); 2.82, 2.88 (s, s, 2 × 3H, N-$(CH_3)_2$); AB-System: ν_A = 3.2, ν_B = 3.4, J_{AB} = 16 Hz, S-CH_2-CO); 1.45, 1.49 (s, s, 2 × 3H, S-C$(CH_3)_2$-).
16	5.75 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.84, 3.88 (s, s, 1H, CO-CH-NH_2); 3.7 (m, 4H, N-$(CH_2)_2$-); 3.38 (m, 1H, H_{11}); AB-System: ν_A = 3.21, ν_B = 3.29, S-CH_2-CO, J_{AB} = 16 Hz); 2.32 (s, 3H, N-CH_3).
17	5.61 (d, 1H, H_{14}, J_{H14H13} = 9 Hz); 3.84, 3.86 (s, s, 1H, COCH-NH_2); 3.7 (m, 4H, N-CH_2); 2.4 (m, 4H, N-CH_2); 2.31 (s, 3H, N-CH_3); 1.36 (s, 6H, S-C$(CH_3)_2$-); 3.41 (d, 1H, H_{11}, J_{H11H10} = 7 Hz).
18	5.61 (d, 1H, H_{14}H, J_{H14H13} = 8,75 Hz); 3.85, 3.87 (s, s, 1H, CO-CH-NH_2); 3.6 (m, 4H, >N-CH_2); 2.9 (m, 4H, >N-CH_2); 3.42 (d, 1H, H_{11}, J_{H11H10} = 6.25 Hz); 2.4 (m, 1H, H_{10}).

19,22 5.75 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.76 (s, 3H, $COOCH_3$); 3.15 (s, 1H, N–CH–CO); 3.32 (s, 2H, S–CH_2–CO); 2.38 (s, 3H, N–CH_3).

20 7.2 (m, 1H, NH); 5.66 (d, 1H, H_{14}, J_{H14H13} = 8,1 Hz); 3.42 (d, 1H, H_{11}, J_{H11H10} = 6,3 Hz); 3.4 (s, 1H, NH–CH–CO); AB–System: ν_A = 3,22, ν_B = 3,34, J_{AB} = 15,3 Hz); 1.42, 1.48 (s,s, 2 × 3H, S–$C(CH_3)_2$); 1.4, 0.96 (s,s, 2 × 3H, $(CH_3)_{15}$, $(CH_3)_{18}$).

21 5.77 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.1 Hz); 3.72 (s, 3H, $COOCH_3$); 3.39 (s, 2H, S–CH_2–CO); 3.28 (s, 1H N–CH–CO); 2.42 (s, 6H, –$N(CH_3)_3$); 1.4, 1.2 (s, s, 2 × CH_3, $(CH_3)_{16}$, $(CH_3)_{18}$).

24 6.38 (m, 1H, NH); 5.62 (d, 1H, $H_{14)}$, J_{H14H13} = 9 Hz); AB–System: ν_A = 3.40, ν_B = 3.47, S–CH_2–CO, J_{AB} = 15 Hz); 3.34 (m, 2H, N–CH_2–CH_3); 2.94 (s, 1H, CO–CH–$N(CH_3)_2$); 2.45 (s, 6H, $N(CH_3)_2$).

25 5.62 (d, 1H, H_{14}, J_{H14H13} = 9 Hz), AB–System: ν_A = 3.39, ν_B = 3.46, S–CH_2–CO, J_{AB} = 15 Hz); 2.48 (s, 6H, N–$(CH_3)_2$).

28 5.76 (d, 1H, H_{14}, $J_{H14,H13}$ = 8.5 Hz); (3.35 (s, 1H, H_2N–CH–CO–); 2.825 (d, 3H, $NHCH_3$, J = $5H_3$); AB–system–CO–CH_2–S–group position of lines 3.29; 3.23; 3.2; 3.14.

The required new starting materials may be obtained as follows:

(A) *3-Methyl-3-mercapto-2-aminobutyric acid (2-hydroxyethyl)amide (for Example 1,3):*

(a) *2,2,5,5-Tetramethyl-3-formyl-4-(4-nitrophenyloxycarbonyl)thiazolidine*

21.7 g of the N-formyl protected acetone adduct of penicillamine, 14.6 g of 4-nitrophenol and 22.7 g of N,N'-dicyclohexylcarbodimide are dissolved in ethylacetate and maintained at 25° for 24 hours. After working-up and chromatography over silica gel (eluant: hexane/ethylacetate = 2/1) a colourless oil is obtained which crystallises out.
NMR ($CDCl_3$): 8.35 (s, 1H, N–CHO); 8.2 (d, 2H, arom. H, J = 8 Hz); 7.25 (d, 2H, arom. H, J = 8 Hz); 4.92 (s, 1H, N–CH–CO); 1.92 (s, 6H, 2 × CH_3); 1.6, 1.75 (s, s, 2 × CH_3).

(b) *2,2,5,5-Tetramethyl-3-formyl-4-hydroxyethylaminocarbonylthiazolidine*

A solution of 1.3 g of 2,2,5,5-tetramethyl-3-formyl-4-(4-nitrophenyloxycarbonyl)thiazolidine and 0.48 ml of ethanolamine in 50 ml of benzene are maintained at 25° for 20 hours. After filtration of the precipitate the benzene solution is concentrated by evaporation and the residue taken up in ethylacetate. To remove the remaining 4-nitrophenol the solution is repeatedly shaken with water and then evaporated to dryness. After chromatography over silica gel (eluant: $CHCl_3/CH_3OH$ = 7/1) the title product is obtained as a colourless oil.
NMR ($CDCl_3$): 1.46, 1.6, 1.92, 1.97 (s,s,s,s, 4 × 3H, CH_3); 5.66 (s, 1H, N–CH–CO); 3.45 (m, 2H, –CH_2–N–); 3.7 (m, 3H, CH_2–O–, OH); 8.35 (s, 1H, H–C = O); 7.17 (t, 1H, –NH–CO, J = 5.4 Hz).

(c) *3-Methyl-3-mercapto-2-aminobutyric acid-(2-hydroxyethyl)amide*

2.6 g of 2,2,5,5-Tetramethyl-3-formyl-4-hydroxyethylaminocarbonylthiazolidine are taken-up in 150 ml of methanolic HCl and maintained at 25° for 18 hours. After removal of the solvent the residue is again taken-up in 0.1 N HCl and the mixture heated at 100° for 15 minutes. After working up the title compound is obtained in free form.
NMR (D_2O): 3.98 (s, 1H, N–CH–CO); 3.2–3.7 (m, 4H, N–CH_2–CH_2–OH); 1.47, 1.52 (s,s, 2 × CH_3).

The following compounds can be prepared analogously.

(B) *3-Methyl-3-mercapto-2-aminobutyric acid amide (for Example 4):*
NMR (D_2O): 4.0 (s, 1H, H_2N–CH–CO); 1.52 1.58 (s, s, 2 × CH_3).

(C) *3-Methyl-3-mercapto-2-aminobutyric acid methylamide (for EX. 5,15)*
NMR (D_2O): 3.84 (s, 1H, H_2N–CH–CO); 2.73 (s, 3H, N–CH_3); 1.38, 1.43 (s, s, 2 × CH_3).

(D) *3-Methyl-3-mercapto-2-aminobutyric acid-(2-aminoethyl)amide (for Example 6):*
NMR (D_2O): 3.95 (s, 1H, H_2N–CH–CO); 3.1–3.7 (m, 4H, –NH.CH_2–CH_2–NH_2); 1.43, 1.49 (s, s, 2 × CH_3).

(E) *3-Methyl-3-mercapto-2-aminobutyric acid-(n)-butylester (for Ex. 8)*
NMR (D_2O): 4.13 (s, 1H, H_2N–CH–CO); 4.25 (t, 2H, –COO.CH_2–); 1.5, 1.56 (s, s, 2 × CH_3).

(F) *3-Methyl-3-mercapto-2-aminobutyric acid-(2-diethylaminoethyl)-amide (for Example 13)*
NMR ($CDCl_3$): 4.0 (s, 1H, NH–CH–CO; 3.7 (m, 2H, CONH–CH_2); 3.3 (m, 2H, CH_2–N–(CH_2–CH_3)$_2$); 1.52, 1.48 (s, s, 2 × CH_3, S–C(CH_3)$_2$); 1.32 (t, 2 × 3H, N–(CH_2CH_3)$_2$, J = 7.2 Hz).

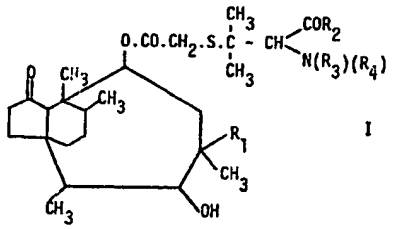
(G) *3-Methyl-3-mercapto-2-aminobutyric acid dimethylamide (for Ex. 14)*:
NMR (D_2O): 4.4 (s, 1H, NH–CH–CO); 3.12, 3.95 (s, s, 2 × 3H, N–(CH_3)$_2$); 1.44 1.35 (s, s, 2 × 3H, S–C(CH_3)$_2$).

(H) *3-Methyl-3-mercapto-2-amino-1-(4-methylpiperazinyl)-butyric acid (for Example 16, 17)*:
NMR (D_2O): 3.65 (m, 4H, N–(CH_2)$_2$); 2.4 (m, 4H, N–(CH_2)$_2$); 2.32 (s, 3H, N–CH_3); 1.35, 1.44 (s, s, 2 × 3H, S–C(CH_3)$_2$).

(I) *3-Methyl-3-mercapto-2-amino-1-piperazinylbutyric acid (for Ex. 18)*:
NMR (D_2O): 3.8 (m, 4H, N–(CH_2)$_2$); 3.3 (m, 4H, N–(CH_2)$_2$); 1.46, 1.44 (s, s, 2 × 3H, S–C(CH_3)$_2$).

CLAIMS

1. Compounds of formula I



I

wherein
R_1 represents ethyl or vinyl
R_2 represents lower alkoxy, amino, lower alkylamino which may be unsubstituted or substituted by amino, lower alkylamino, di-(lower)-alkylamino or hydroxy, di-(lower)-alkylamino or a five or six membered, saturated heterocycle which contains one or two nitrogens as heteroatoms and which may be unsubstituted or substituted by lower alkyl and
R_3 and R_4 represent, independently, hydrogen or lower alkyl, in free base or acid addition or quaternary salt form.

2. A compound as claimed in claim 1 wherein R_2 represents lower alkoxy, amino, optionally amino or hydroxy substituted lower alkylamino or a di-(lower)-alkylamino group and R_1, R_3 and R_4 are as defined in claim 1 in free base or acid addition or quaternary salt form.

3. A compound as claimed in claim 1 or 2 wherein R_2 represents amino, lower alkylamino or lower alkoxy in free base or acid addition or quaternary salt form.

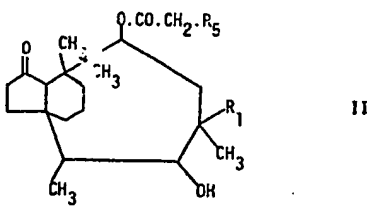
4. A compound as claimed in any one of claims 1 to 3, wherein R_3 and R_4 represent hydrogen or lower alkyl in free base or acid addition or quaternary salt form.

5. A compound as claimed in claim 4 wherein R_3 and R_4 represent hydrogen in free base or acid addition or quaternary salt form.

6. A compound selected from 14–O-[(1-amino-1-methylaminocarbonyl-2-methylpropan-2-yl)-thioacetyl]dihydromutilin and 14–O-[(1-amino-1-methylcarbonyl-2-methylpropan-2-yl)-thioacetyl]-mutilin in free base or acid addition or quaternary salt form.

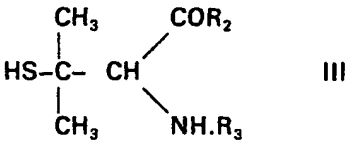
7. A compound as claimed in any one of claims 1 to 6 in (D)-isomeric form.

8. A process for preparing a compound according to claim 1 which comprises reacting a compound of formula II



II

with a compound of formula III



III

whereby R_1, R_2 and R_3 are as defined for formula I and R_5 represents chlorine, bromine or OSO_2R_6 wherein R_6 is alkyl or aryl and if desired further mono- or di-alkylating a compound thus obtained wherein R_3 represents hydrogen or further mono-alkylating a compound thus obtained wherein R_3 represents lower alkyl and recovering the compound thus obtained in free base or acid addition or quaternary salt form.

9. A chemotherapeutic composition comprising a compound according to any one of claims 1 to 7 in free base or chemotherapeutically acceptable acid addition or quaternary salt form together with a chemotherapeutically acceptable diluent or carrier.

10. A compound according to any one of claims 1 to 7 in free base or chemotherapeutically acceptable acid addition or quaternary salt form for use as a chemotherapeutic agent.

11. A compound according to any one of claims 1 to 7 in free base or chemotherapeutically acceptable acid addition or quaternary salt form for use in combating bacteria and obligatory anaerobes.

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